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Review

Plasma membrane and cytoskeleton dynamics during single-cell wound healing☆,☆☆

Eric Boucher, Craig A. Mandato *

Department of Anatomy and Cell Biology, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

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ABSTRACT

Wounding leads not only to plasma membrane disruption, but also to compromised cytoskeleton structures. This results not only in unwarranted exchanges between the cytosol and extracellular milieu, but also in loss of tensegrity, which may further endanger the cell. Tensegrity can be described as the interplay between the tensile forces generated by the apparent membrane tension, actomyosin contraction, and the cytoskeletal structures resisting those changes (e.g., microtubules). It is responsible for the structural integrity of the cell and for its ability to sense mechanical signals. Recent reviews dealing with single-cell healing mostly focused on the molecular machineries controlling the traffic and fusion of specific vesicles, or their role in different pathologies. In this review, we aim to take a broader view of the different modes of single cell repair, while focussing on the different ways the changes in plasmalemma surface area and composition, plasmalemma tension, and cytoskeletal dynamics may influence and affect single-cell repair.

1. Introduction

Recent reviews dealing with single-cell healing have mostly focused on the molecular machineries controlling the traffic and fusion of various vesicles [1], or their role in different pathologies [2]. Little attention has been given to the different ways changes in plasmalemma area, plasmalemma composition, effective membrane tension (defined in [3]) and cytoskeleton dynamics that occur upon wounding, influence and affect single-cell repair.

Tensegrity is a concept used to describe a system in which stable structures are achieved through pre-stress and the interaction of opposing tension and compression elements. In the cell, cytoskeletal actin filaments act as the main tension-bearing and generating element [4], while microtubules act as the main compression-bearing element. Intermediate filaments usually play a more passive role, but may contribute to the tensegrity structure in the case of highly strained cells [5] (the contribution of each cytoskeletal component is reviewed in [6]). Other components such as plasmalemma shape and composition [7,8], membrane in plane tension [3,7], tether force (i.e., force linked to plasmalemma to cortex attachments) [3],contacts with the extra-cellular matrix (ECM), cell–cell contacts, shear stresses, stretch stresses, or even hydrostatic pressure, may also be involved in cellular tensegrity (reviewed in [6,9]). The same forces may also modify the "tensegral" stability of the cell, resulting in mechanotransduction [9,10], which in turn control many biological processes.

Damaged cells are able to restore the plasmalemma barrier function through addition of membrane material to the plasmalemma surface, dynamic changes in the shape of the plasmalemma [11] and by restoring normal cytoskeletal structures (e.g., via the formation of an actomyosin purse-string [12–17]). As such, in addition to restoring the barrier function of the cell membrane, single cell wound healing can also be viewed as an attempt at restoring tensegrity to the wounded cell.

In this review, we aim to take a broader view of the different mechanisms that have been proposed for single cell wound healing, while focussing the attention on the different ways plasmalemma area, plasmalemma shape, and cytoskeleton dynamics may influence and affect single-cell repair.

2. Spontaneous resealing of "relaxed" simple membranes

Studies done with artificial lipid bilayers and erythrocyte ghosts provide a model where the resealing of small membrane disruptions is a thermodynamically-favored, primarily lipid-related event [18]. This spontaneous resealing occurs within microseconds [19], and is contingent on low in plane membrane tension [20] (i.e., tension created by the lipid bilayer). It involves the removal of the hydrophobic domains of phospholipid molecules from the newly aqueous environment created by membrane damage and the lateral movement of phospholipid to

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* Corresponding author at: 3640 University, Strathcona Anatomy and Dentistry Bldg, Room W-309, Montreal, Quebec H3A 2B2, Canada.
E-mail address: craig.mandato@mcgill.ca (C.A. Mandato).

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reseal the wound site [21,22]. Membrane lipid composition [21,22], concentration of divalent ions such as Ca^{2+} [23], association with proteins [24], and wound radius [20] have all been identified as having direct effect on the speed of spontaneous membrane resealing. Closure of pores in bilayer membranes is not only a factor of membrane surface tension, but also of the line tension that is a function of pore size [25]. This also explains why artificial liposomes or erythrocyte ghost do not spontaneously reseal under physiological conditions [26] and may even increase in size or lyse the liposome [25] or erythrocyte ghost [18]. Neither the liposome or erythrocyte ghost possesses the tools necessary to actively modulate apparent membrane tension, whether it is at the membrane surface (through addition of endomembrane components to the cell surface) or from the inside (thought the modulation of tether forces).

3. Sensing cell damage

While they provide valuable insights into the mechanism of cell repair, liposomes and erythrocyte ghosts frequently do not represent the behavior of many cell types. For example, cells readily heal very large membrane and cytoskeletal disruptions using a variety of processes that require a series of dynamic plasmalemma and cytoskeletal modifications. In order to repair, however, cells must first detect the damage. Therefore, damage detection is crucial to the survival of damaged which is achieved by a variety of sensors described in the following sub-sections.

3.1. Ca^{2+} sensors

Synaptic exocytosis [27], sperm capacitation [28], surfactant secretion [29] and cytokinesis [30] all involve Ca^{2+}-dependent dynamic changes in the composition and structure of the plasmalemma, cytoskeleton, or both. It is therefore not surprising that the same families of proteins involved in the Ca^{2+}-dependent mechanisms previously described are also used in the detection of cell damage and the initiation of single-cell repair.

The Ca^{2+}-binding proteins involved in wound healing can be divided according to the structural domain of their calcium-binding site(s). Each group of Ca^{2+}-binding protein acting as a sensor during single-cell wound healing is discussed below and summarized in Table 1.

3.1.1. C2-domain containing proteins

The C2 domain was first identified in the conventional protein kinase C (PKC) (reviewed in [31]), and were later found in a variety of proteins at the center of many Ca^{2+}-induced vesicular traffic events. For example, synaptotagmin I, which contains two C-terminal C2-domains, has been shown to control Ca^{2+}-triggered exocytosis of synaptic vesicles (reviewed in [32]) through its interaction with phosphatidylinositol 4,5 bisphosphate (PIP_2) and soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE) complexes of the synaptic membrane (reviewed in [33]). Otoferlin, a member of the ferlin family (reviewed in [34]), contain multiple C2 domains, and is known to be the Ca^{2+}-sensor involved in SNARE-mediated synaptic release that controls hearing [35]. Single-cell repair has also been shown to involve exocytosis; SNARE complexes, and members of the synaptotagmin and ferlin families have also been shown to be involved in membrane resealing. Indeed, embryonic fibroblasts from synaptotagmin VII-deficient mice show diminished susceptibility to *Trypanosoma cruzi* invasion, but are defective in lysosomal exocytosis and resealing after wounding [36], which suggest impaired Ca^{2+}-mediated lysosomal exocytosis [37]. Synaptotagmin-deficient cells or cells treated with antibodies raised against the C(2)A domain of synaptotagmin show markedly lower membrane repair in stretch-based wounding assays [36]. Muscle dystrophies are associated with decreased sarcolemma wound healing, and mutations in the gene coding for the ferlin family member, dysferlin, have long been shown to be associated with Miyoshi myopathy [38], Duchesne muscular dystrophy [39], and limb girdle muscular dystrophy (LGMD) type 2B (LGMD2B) (reviewed in [40]). Similarly, following laser-induced membrane damage, dysferlin-deficient muscle fibers are defective in Ca^{2+}-dependent sarcolemma resealing compared to wild type controls [41].

Calpains are Ca^{2+}-dependent, intracellular cysteine proteases, that possess a "C2-like" domain located next to the N-terminal protease core domain [42]. Unlike other proteolytic systems, calpains directly target specific proteins. Their proteolytic activity does not necessarily result in the degradation of their targets, but in the activation, inhibition, altered activity of their targets [42]. Mutations in the muscle-specific calpain-3, have been associated with LGMD2A [40]. Cells in which m-calpain and μ-calpain activity have been shut down, show decreased survival and fail to recover after laser-induced membrane disruption [43].

3.1.2. EF-hand domain-containing proteins

The protein coded by the apoptosis-linked gene (ALG)-2 contains five serially repetitive EF-hands, and is the most conserved member of the penta-EF hand protein family [44]. Upon Ca^{2+}-binding, ALG-2 undergoes conformational changes that allows it to interact with proline-rich proteins, such as annexin VII and annexin XI [45],as well as the endosomal sorting complex required for transport (ESCRT) protein, tumor susceptibility gene 101 (TSG101) [46], and the ESCRT-associated, ALG-2-interacting protein X (ALIX) [47]. Members of ESCRT, have been known to organize the plasmalemmal deformation and scission events involved in the formation of multivesicular endosomes, the shedding of enveloped viruses, and cytokinesis (reviewed in [48]). Knockdown of ALG-2 expression increases the number of cells that fails to survive laser injury [49].

S100 proteins constitute a large group of EF-hand, Ca^{2+}-binding proteins [50]. S100 proteins are involved in a variety of physiological events including modulation of enzymatic activities, reorganization of cytoskeletal components, protein traffic, and vesicular traffic (reviewed in [50]). They have been shown to be upregulated in a variety of metastatic cancers [2,51], and may play a role in cytoskeletal remodeling and plasma membrane repair [2]. S100A10 forms a Ca^{2+}-dependent asymmetric heterotetramer with annexin II [52,53], which has been shown to be involved in several single cell repair events involving dysferlin (see Section 5.3.2) or ANAHK (see Section 5.3.3) (Table 2).

3.1.3. Annexins

Annexins constitute a large family of proteins that binds negatively charged phospholipids in a Ca^{2+}-dependent manner. Some annexins such as annexin VI, can also associate with lipid rafts, and bind the actin cytoskeleton [54]. As such, it is not surprising that annexins are involved in fusogenic events [55], pinocytotic rocketing [56], plasma membrane reorganization [57], and cytoskeleton dynamics [58]. Contrary to synaptotagmins, ferlins or calpains, evidence for the involvement of annexins in single-cell repair has mainly been gathered through experimental evidence (reviewed in [59]). Nonetheless, mutations in annexin VI have recently been shown to act as a negative modifier in a mouse model of muscular dystrophy [60]. Similarly, annexin II has been shown to be mutated in patients suffering from a non-dysferlinopathic form of Miyoshi myopathy [38].

3.2. Dynamic changes of the plasmalemma as damage signals

Cell damage disrupts normal membrane lipid polarization and organization, and the plasma membrane surrounding the wound is further modified by transient de novo synthesis or the transport and delivery of different lipids, at specific areas of, or around the wound site [61]. Therefore, the dynamic changes of the plasmalemma that occurs during wound healing should be considered as genuine cell damage signals. For example, the release of acid sphingomyelinase (ASM) that follows Ca^{2+}-dependent lysosomal exocytosis produces ceramide-rich

Table 1
Ca^{2+} sensors involved in single-cell wound healing.

$Ca^{2\pm}$ sensors	Proof of involvement in membrane repair	References
C2 domain		
Calpains		
μ-Calpain, m-calpain, calpain-3	– General calpains inhibitors (capleptin and calpastatin) impair calcium-dependent wound healing after scrape-induced injury. – siRNA knockdown of calpain-1 and calpain-2 genes impair calcium-dependent wound healing after scrape-induced injury. – Calpain-$4^{-/-}$ cells, which do not express Calpain-1 or Calpain-2, show decreased survival and fail to recover after laser-induced membrane disruption. – Loss-of-function mutations of the calpain-3 gene causes LGMD2A.	[43,97,119,126, 127,195,196]
Ferlins		
Dysferlin	– Muscle-cells of dysferlin-null mice fail to undergo Ca^{2+}-dependent membrane resealing after laser-mediated injury. – Mutations of the dysferlin gene are associated with Miyoshi myopathy, Duchesne muscular dystrophy, and LGMD2B.	[38–41,197]
Myoferlin	– Mouse epithelial cancer cell line treated with anti-myoferlin siRNA, show greater plasma membrane damage than cells treated with non-specific siRNA.	[197–201]
Synaptotagmins		
Synaptotagmin VII	– Recombinant synaptotagmin VII C(2)A domain or function-blocking antibodies inhibits membrane resealing. – Synaptotagmin VII-deficient mice show impaired lysosomal-mediated exocytosis and membrane resealing.	[36,108,110]
EF-hand domain		
PEF family		
ALG-2	– Knockdown of ALG-2 expression increases the number of cells that fails to survive laser injury. – ALG-2 is necessary for the assembly of the ESCRT-III–Vsp4 complex, involved in shedding of damaged portion of the plasmalemma.	[49]
S100 family		
S100A10[a]	– S100A10 depleted cells show increased cell damage and reduced membrane repair.	[136–138]
S100A11	– S100A11 mutants unable to bind annexin II show diminished plasmalemma repair and survival in a cellular model of invasive cancer.	[51]
Others		
Annexins		
Annexin I	– Annexin I function-blocking antibody, peptide competitor, and a dominant-negative annexin I incapable of Ca^{2+}-binding, all inhibit membrane resealing.	[202,203]
Annexin II	– siRNA knockdown of annexin II leads to a decrease of enlargosome-mediated exocytic membrane repair.	[134,204,205]
Annexin V	– Cells expressing a mutated form of annexin V show impaired wound repair.	[72]
AnnexinVI	– Cells expressing a truncated form of annexin VI show impaired wound repair.	[60,204,206,207]

[a] S100A10 is constitutively active and does not bind Ca^{2+} [52].

domains. These domains change the binding affinities of annexins [62] and caveolins [63] for the plasmalemma, affect cytoskeleton dynamics [64] and results in changes in plasmalemma architecture that plays an important role in the progression of membrane repair (discussed in Sections 5.4.1 and 5.4.2).

A recent study in *Xenopus* oocytes [61] have also shown that wounding induces the formation of micrometer-scale PIP_2-, phosphatidylinositol 3,4,5 trisphosphate (PIP_3)- and phosphatidylserine (PS)-, phosphatidic acid (PA)-, and diacylglycerol (DAG)-enriched domains. PIP_2, PIP_3, and PS moved towards the wound edge, with PS concentrating in a zone closest to the wound edge, near an area of high Ras homolog gene family, member A (RhoA) activity (see Section 6). As for PIP_2 and PIP_3, they can be observed within a zone of high cell division control protein 42 homolog (Cdc42) activity (see Section 6). On the other hand, DAG and PA were both shown to immediately segregate at the wound site, in a zone overlapping the zones of RhoA and Cdc42 activity. Since DAG is known to be able to recruit PKCβ and PKCη [65], the authors suggested that generation of DAG at the wound site could therefore act as an upstream signal for the regulation of RhoA and Cdc42 zones and ultimately the formation of the actomyosin ring that characterizes the end of the wound healing process (see Section 6). Vaughan et al. also stated that DAG was mainly derived from phosphatidylcholine specific phospholipase C (PC-PLC) hydrolysis of phosphatidylcholine (PC) and from sphingomyelin synthase (SMS) activity, whereas PA was shown to be mainly produced via PLC. The phospholipase D (PLD)-derived PA contribution to the DAG pool is harder to judge since DAG can also be synthesized from PA by phosphatidic acid phosphohydrolase and their use of a PLD inhibitor would also increase the availability of PC for PC-PLC. Nevertheless, blocking generation of DAG, but not PA, was shown to inhibit Rho and Cdc42 activation, as well as wound closure.

Interestingly, wounding cultured keratinocytes by lifting them from their substratum leads to increased PLD2 activation and a paradoxical diminished phosphatidylglycerol (PG) production [66]. The authors proposed that the apparent diminished PG production was due to the disruption of the functional interaction of PLD2 with aquaporin-3 [67], or a previous PG-deficiency in the wounded cells. While exogenous

Table 2
Key molecular players of injury-related, Ca^{2+}-dependent exocytosis.

$Ca^{2\pm}$-dependent exocytosis mechanism	Vesicular compartment(s)	Key molecular players	References
Dysferlin-dependent exocytosis	MG53-rich vesicles Dysferlin-rich vesicles Lysosomes (?)	Dysferlin, calpains, MG53, Caveolin 3 Annexin II:S100A10:AHNAK complex (?)	[43,74,115,119,122,123]
Synaptotagmin-dependent exocytosis	Conventional lysosomes	Synaptotagmin VII, Syntaxin-4, SNAP-23, and Vamp-7	[104,108,110,111,190]
AHNAK-dependent exocytosis	Enlargeosomes	AHNAK and S100A10:Annexin II heterotetramer. AHNAK, syntaxin 6, SNAP-23 and Vamp-4 Calpain-3 Dysferlin(?)	[130,134–140,143,191,192]
Facilitated exocytosis	Trans-golgi network	Protein kinase C	[87,101]
Potentiated exocytosis	?	Nitric oxyde signaling Cyclic adenosine monophosphate response element binding protein	[193,194]

glycerol [68] and PG [66] were shown to be able to rescue the delayed wound healing phenotype of aquaporin-3 KO mice [69], the role of PG and PLD2 in wound healing could also be linked to other PLD-derived lipids such as PA and DAG. This would be particularly interesting as it would be compatible with the DAG-rich zone observed by Vaughan et al. [61].

4. "Stop gap" measures of wound healing

4.1. Plasmalemma stabilization at the wound site

As discussed in Section 2, the wounded membrane is subjected to substantial tension forces that arises from the in plane membrane tension of the lipid bilayer, line tension around the wound edge, as well as the tether force created by membrane-to-cortex attachments and cytoskeletal proteins such as cortical actin [8]. This increased apparent membrane tension should result in the expansion of the wound. This however rarely happens in healthy cells. Stabilization of the injured membrane might thus play a preliminary role in the repair process.

Annexin V binds membrane phospholipids upon Ca^{2+}-activation, where it can rapidly self-assemble into two-dimensional (2D) arrays [70]. Annexin V arrays are known to be able to cluster phospholipids, and in vitro studies suggest that such arrays rigidify lipid monolayers as well as reduce the lateral diffusion of phospholipids [71]. As such, annexin V array could provide a counteracting force to the tether forces generated by the underlying cytoskeleton. While the relative importance of wound stabilization by annexins to plasmalemma resealing has yet to be fully demonstrated, a good case for it can be found in a series of experiments involving a mutant form of annexin V that is unable to form trimers or 2D arrays, but retains virtually identical phospholipid binding characteristics [72]. Laser-wounding assays performed on perivascular cells, showed that exogenous mutant annexin V was unable to rescue normal wound healing in annexin V-negative cells, while exogenous native annexin V is able to [72]. It is important to note that this model is not in competition with the other more traditional roles of annexins in cell repair discussed in the rest of this review. Indeed, annexin V 2D arrays present open structures and have been shown to form heterogeneous assemblies with annexin I and annexin II [73]. Mitsugumin 53 (MG53), also known as tripartite motif-containing protein 72 (TRIM72), has also been proposed to stabilized the wound through oligomerization [74] and by its interaction with mini-dysferlin$_{c72}$ and caveolins (see Section 5.3.2). Similar protection has also been proposed during the rapid binding of ESCRT proteins which produces membrane deformations that may help stabilize the wound [75] (see Section 5.5.2).

4.2. Plugging the hole: "membrane patch"

Considering the relatively high apparent membrane tension present at the wound site, one might ask how cells are able to heal wounds so rapidly. A first clue came with the study of damaged sea urchins [76]. Ca^{2+} was shown to induce rapid homotypic fusion of specialized intracellular vesicles, the yolk granules [77], leading to the formation of a large membrane patch that is able to cover very large wounds (>1000 μm^2) [76]. Heterotypic fusion of the newly created large vesicles with the edges of the wounded plasmalemma has also been observed [78], and has been presumed to complete the resealing process. The formation of an underlying "membrane-patch" is likely a stop-gap measure of single cell repair, aimed at rapidly rescuing membrane function, at the expense of local membrane composition and shape [77]. The patch is removed via the rapid formation of large endosomes in a process that is not directly dependent on intracellular Ca^{2+} or microtubules, but involves the actin cytoskeleton [79] and the closure of an actomyosin string-purse assembly that characterizes the end of the wound healing process in *Xenopus* oocytes, sea urchin oocytes and *Drosophila*.

The membrane patch model of single-cell repair requires a very large pool of readily available cytosolic membrane components, a situation most exemplified by the yolk granules found in oocytes. While formation of a "membrane patch" was historically proposed to be involved in the repair of most somatic mammalian cells, other mechanisms involving the Ca^{2+}-dependent exocytosis and endocytosis have since been proposed and are discussed in the rest of this review.

5. Plasmalemma protection and repair: a game of tension

5.1. Direct responses of the plasmalemma to changes in apparent membrane tension

Caveolae are a specialized form of lipid-raft, of distinctive size (50–100 nm) and concave structure. The exact molecular events leading to caveolae assembly is still somewhat unclear, but involves the stabilization of lipid rafts by caveolin oligomers and the formation of large complexes composed of caveolins, cavins and other accessory proteins (reviewed in [80]). Caveolae have long been known to flatten in response to mechanical stretch [81], and disruption of caveolae with methyl-β-cyclodextrin, a compound known to disrupt caveolae, diminishes the time to cell lysis upon hypotonic challenge [82]. Caveolae can thus be viewed as a "membrane buffer" that limits increases in apparent membrane tension by diminishing the in plane tension without the need of additional membrane components from Ca^{2+}-dependent exocytosis. Instead, additional membrane area is produced by the rapid flattening and disassembling of caveolae upon mechanical stress [83], which are rapidly reassembled once the mechanical stress is released [83]. Mutations in the caveolin-3 gene are involved in the pathogenesis of several forms of LGMD, regrouped under the LGMD1C denomination [40]. Caveolin-3 deficient mice also exhibit robust muscular degeneration [84]. The relative contribution of caveolae to protection against stretch-induced mechanical deformation is difficult to judge as caveolin-3 is essential for dysferlin-mediated exocytosis (see Sections 5.3.2), and for endocytosis-mediated repair (see Section 5.4). An attractive, albeit speculative, hypothesis would be that pre-existing caveolae could also passively potentiate plasmalemma repair by releasing apparent membrane tension near the wound edge, a site of initial high membrane tension because of both high line tension and high tether forces.

5.2. Cytoskeletal depolymerization: decreasing tension and preparing for vesicular transport

The cytoskeletal actin network is intimately attached to the plasma membrane, and this tether force is partly responsible for the high apparent membrane tension experienced by the plasma membrane [85]. Therefore, efficient membrane resealing must include a tension-releasing step that involves diminished cytoskeletal association with the plasmalemma or dynamic changes in cortical cytoskeleton structure. In addition, plasmalemma resealing requires the participation of intracellular vesicles which may not necessarily be pre-docked to the plasmalemma [86]. As such, the intracellular vesicles participating in plasmalemmal repair must be actively transported to the wound site where they may undergo homotypic or heterotypic fusion with the plasmalemma (see Sections 4.2 and 5.3). The presence of an intact cortical cytoskeleton would therefore hinder vesicular transport, fusion events (see Sections 4.2 and 5.3), and subsequent endocytic (see Section 5.4) or blebbing events (see Section 5.5). Indeed, local actin cytoskeleton depolymerization and subsequent repolymerization have also been shown to be necessary for exocytic or endocytic repair of oocytes [76], as well as unpolarized [87] and polarized [88] mammalian cells.

Considering its importance for wound healing, it is worthwhile to examine the several factors that have been shown to control the actin cytoskeleton dynamic during the early phase of single-cell repair. First, a sustained and broadly localized secondary disruption of the actin

cytoskeleton was shown to follow the initial mechanical disruption of the actin cytoskeleton [89]. The increased Ca^{2+} concentration that accompanies plasmalemma disruptions also directly contribute to actin depolymerization, as it is able to induce actin depolymerization in a variety of acellular systems [90,91]. Similarly, permeabilization of cells by the bacterial transmembrane pore streptolysin O (SLO) leads to an increase of intracellular Ca^{2+} in the absence of a mechanical wound or of significant plasmalemma disruption. Alternatively, the substantial changes of tensegrity experienced by the damaged cell might also induce mechanotransduction signals leading to actin depolymerization. Indeed, mechanical signals originating from focal adhesions (reviewed in [92]) and stress fibers (reviewed in [93]) are known to induce actin depolymerization through the activation of mechanosensitive ion channels [94], RhoA signaling [95], via the direct mechanosensing ability of polymerized actin [93], or of the actin-binding protein cofilin (reviewed in [96]). As stated previously, calpain-deficient cells are more susceptible to scrape-induced damage, due to impaired wound healing [97]. While calpains have been shown to be involved in dysferlin-mediated exocytic membrane resealing (see Section 5.3.2), this impairment could also be attributed to the role calpains play as cytoskeleton architecture regulators. Indeed, calpains were shown to be responsible for the Ca^{2+}-dependent degradation of vimentin and talin upon scrape injury of various fibroblast cell lines [97]. Talin is a large homodimeric protein present at focal adhesion sites. Calpains have been shown to cleave talin into a large globular head that directly binds integrins, PIP_2 and focal adhesion kinases, and a rod domain that binds vinculin and actin (reviewed in [98]). Its degradation by calpains upon wounding would therefore be compatible with the cytoskeletal remodeling that follows membrane disruptions. Finally, actin binds to PS, which is found to be preferentially found on the inner leaflet of the plasmalemma [99]. As such, the loss of polarization associated with plasmalemma damage [100], may also contribute to the actin depolarization associated with plasmalemma repair. For the same reason modifications of plasmalemma composition associated with the exocytic events of early plasmalemmal repair (see Section 5.3) may also accelerate large-scale actin cytoskeleton depolymerization.

Consistent with the idea that disruption of cytoskeletal structures around the wound facilitates vesicular transport and fusogenic events, it is worth noting that plasmalemma disruptions can also induce disassembly of microtubules around the wound site [101]. Disassembly is Ca^{2+}-dependent, and is probably achieved by promoting the catastrophe reaction through the direct interaction of Ca^{2+} and microtubules [102]. The role of microtubule disruption is still somewhat unclear, however their recruitment and elongation around the wound site [101] has been shown to be implicated in the lysosomal transport and in lipid traffic from the trans-Golgi network (TGN) that characterizes the facilitated response of membrane resealing [87,103,104].

5.3. Exocytosis: the endgame of plasmalemma repair or just a phase?

By comparison to *Xenopus* or sea urchin oocytes, mammalian cells experience comparatively smaller wounds, take longer on average to restore their barrier function, and possess a relatively smaller vesicle pool. This suggests that mammalian cells do not rely as heavily "patch" formation as is observable in oocytes models. Mammalian cells also heal repeated plasmalemma disruptions more rapidly [103,105], which is difficult to explain under the classic "patch" model.

The Ca^{2+}-dependent exocytosis events that accompany plasma membrane repair in mammalian cells has been shown to lead to increased plasmalemma area [106], and decreased apparent membrane tension [87]. This would be compatible with a model in which the plasmalemma is mostly healed through the heterotypic fusion of cytosolic vesicles and the plasmalemma, rather than homotypic fusion events involved in the "patch" model. The decreased apparent membrane tension afforded by the combined effect of the exocytic addition of membrane components to the plasmalemma, and of cytoskeletal disassembly, could then promote resealing by increasing the lateral movement of membrane phospholipid, thus favoring their spontaneous fusion with the other wound edge or nearby vesicles. This " tension-mediated" model of membrane resealing is compatible with the fact that treatment with either cytochalasin D (an actin polymerization inhibitor) [87,103], or surfactant [103], both rescue membrane resealing in tetanus toxin- and botulinum neurotoxin A and B-treated cells. Tetanus toxin and botulinum neurotoxins A and B are known to inhibit exocytosis of vesicles of lysosomal and of TNG origin by cleaving members of the SNARE complex involved in most vesicle fusion events.

Recent years have also seen the emergence of a new model of cell repair in which the tension release afforded by exocytosis facilitate membrane repair not only trough spontaneous resealing events, but also through endocytic events and membrane invagination (see Section 5.4). Independently of the way it leads to plasmalemma repair, synaptotagmin- and dysferlin-mediated exocytosis leads to plasmalemma repair and therefore merits further attention. Similarly, because of the different nature of enlargeosomes, their contribution to exocytosis-mediated repair will be treated separately in Section 5.3.3. The hallmarks of mode of injury-mediated, Ca^{2+}-dependent exocytosis mechanisms are presented in Table 2 as well as Fig. 1.

5.3.1. Synaptotagmin-mediated repair

Membrane proximal lysosomes have been described as the major vesicles responsible for Ca^{2+}-dependent exocytosis in nonsecretory cells [107] and are also central to exocytotic-repair [108]. In mammalian cells, conventional lysosome involved in plasmalemma repair can be defined as lysosomal-associated membrane protein 1 (LAMP-1)-positive [108], ASM-containing vesicles [109]. They are transported via microtubule-dependent mechanisms [37] to the plasmalemma, where lysosome-bound synaptotagmin VII [110] and vesicle-associated membrane protein (VAMP)-7 [111], interact with plasmalemmal syntaxin-4 and synaptosomal-associated protein (SNAP)-23 [111], which facilitates heterologous fusion.

5.3.2. Dysferlin-mediated repair

Dysferlin share a lot of structural properties with synaptotagmins (see Section 3.1.1) and has even being known to interact with syntaxin-4 [112]. However, dysferlin-mediated exocytosis appears to be more complicated than the ones involving synaptotagmin. Indeed, syntaxin-4 may not even be involved in dysferlin-mediated repair, as it is involved in the endosomal-mediated proteolytic control of the expression of dysferlin to the membrane [112].

It is nonetheless worth noting that while the fusogenic machinery and sequence of events differs, dysferlin-mediated repair shares the same core functions with synaptotagmin-VII/conventional lysosome-mediated repair. Indeed, in both cases cytosolic membrane is delivered to the plasmalemma, leading to ASM release to the outer leaflet [113], and eventually, endocytic repair (see Section 5.4; Fig. 1).

The molecular events involved in dysferlin-mediated exocytosis is somewhat obscured by the sheer number of proteins that are being proposed to be part of the "dysferlin complex". Indeed, dysferlin has been shown to bind or be associated with many proteins such as MG53 [114], caveolin-3 [115], annexin I [116], annexin V [74], as well as many others [117]. Dysferlin has even been shown to associated with the annexin II:S100A10:AHNAK complex, which is involved in enlargeosome exocytosis. Whether dysferlin is involved in enlargeosome exocytosis or enlargeosomes are involved in dysferlin-mediated repair is still open to interpretation (see Section 5.3.3).

Out of all the dysferlin partners identified so far, MG53 has shown to have the most functional impact for dysferlin exocytosis. For example, mutations in MG53 are known to cause LGMD2H [118]. Dysferlin has been shown to interact directly with MG53 through its C2A domain [114], and the interaction of dysferlin and MG53 has been shown to be essential for normal repair of muscle cells after mechanical injuries assays [74]. Finally, several membrane repair defects in muscular

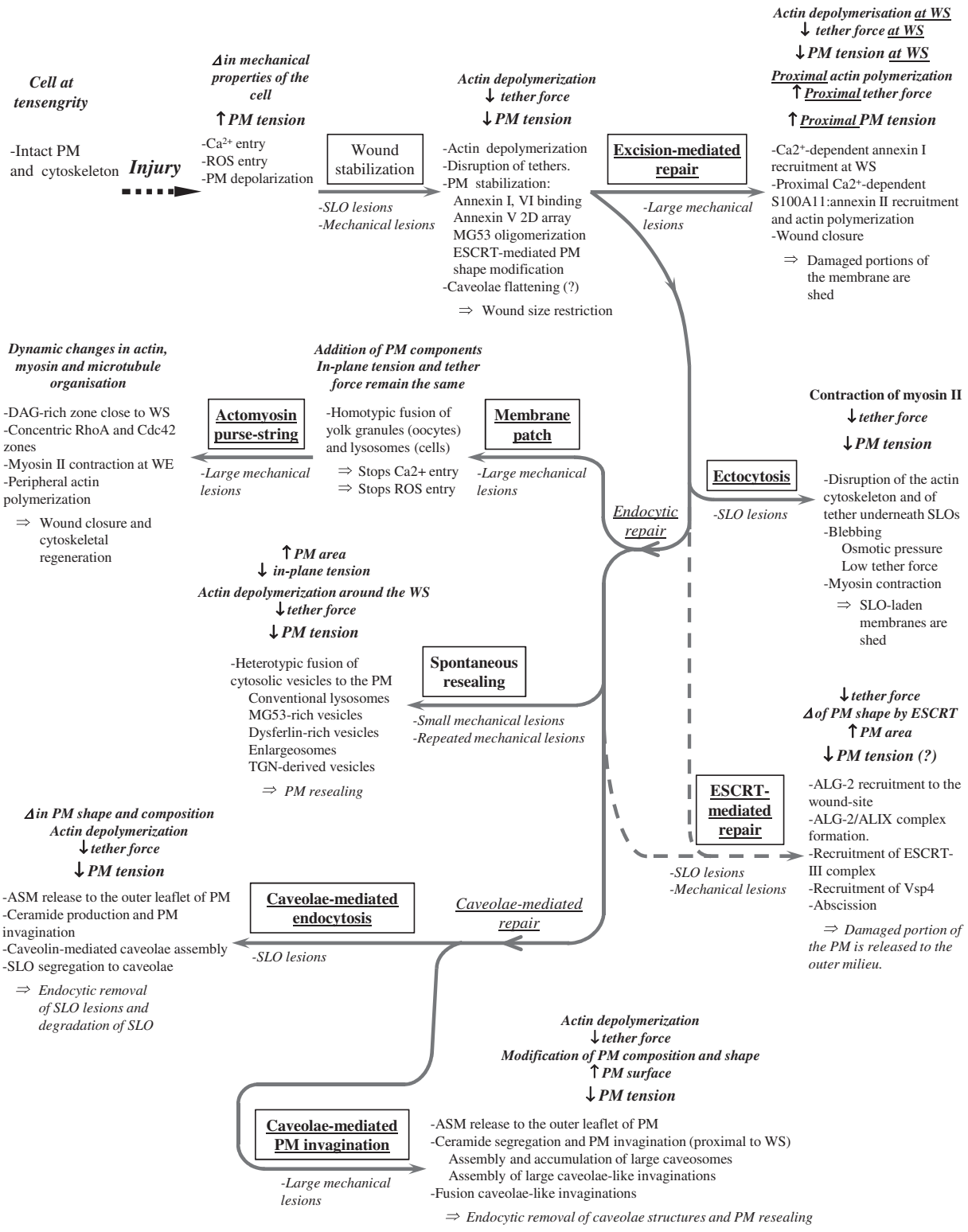

Fig. 1. Single-cell repair. Overview of the different modes of single-cell repair (boxed, underlined and bold) and of their interrelation (plain lines denote known relationships; dashed lines denote relationships that still need to be tested; arrow denotes the direction of the relationship). Information relating to plasmalemma tension or plasmalemma area (bold, italicized) can be found over each repair mode description (regular text). ASM: acid sphingomyelase; SLO: streptolysin O (and other pore-forming toxins); ROS: reactive oxygen species; PM: plasmalemma; Proximal: wound site proximal; tether: plasmalemma-cytoskeleton tether; TGN: trans-Golgi network; WE: wound edge; WS: wound site; ↓: decreased; ↑: increased; Δ: modification.

dystrophy are being linked to mutations altering normal interaction between MG53, caveolin-3, and dysferlin [115]. Nonetheless, the mechanism of dysferlin/MG53 fusion is hard to grasp. Indeed, fusion of dysferlin-rich vesicles to the plasmalemma necessitates prior decoration of the injury site by MG53. However, dysferlin recruitment to the membrane has been shown to occur before that of MG53-rich vesicle [43,114,119]. This is particularly puzzling, since dysferlin is also enriched in the sarcolemma and transverse tubules of uninjured muscle

fibers [120]. MG53, binds membranes through PS [121,122], and can be found at the cytosolic face of the plasmalemma and of specialized vesicles (thereafter called MG53-rich vesicles) of uninjured cells [74,122].

Upon injury, reactive oxygen species from the oxidative extracellular environment cause the oligomerization of not only MG53 found on the borders of the plasmalemmal injury, but also of MG53 found on MG53-rich vesicles [74]. This oxidative oligomerization of MG53-rich vesicles has been shown to account for at least some of the recruitment of MG53-rich vesicles to the wound site [116], but traffic of MG53-rich vesicles has been shown to be mostly Ca^{2+}-dependent [74], and to involve nonmuscle myosin type IIA [123].

The mechanism of dysferlin recruitment to the wound site is also a matter of some interrogation, but involves the formation of dysferlin-rich vesicles of plasmalemmal origin [120], their homotypic fusion via microtubules and kinesin-mediated events [124,125], and their transport from and to the plasmalemma by an actin cytoskeleton-dependent mechanism [120]. Dysferlin-mediated fusion also necessitates processing of dysferlin by calpains into mini-dysferlinC72 [43,119,126]. Dysferlin processing do not involve the muscle-specific calpain-3, but rather μ-calpain and m-calpain, as Caspn3-null mice do not show signs of loss of sarcolemma resealing after needle scratch or laser damage [127]. The function of the rest of the members of the "dysferlin complex" is still somewhat unclear, but many are associated with specific LGMDs (reviewed in [128]). The main binding partner involved in dysferlin-mediated exocytosis are summarized in Table 2.

5.3.3. The role of AHANAK and enlargeosomes

Plasmalemma resealing has been shown to involve exocytosis followed by ASM release, a characteristic of lysosomal exocytosis (see Section 5.3.1) necessary for endocytic (see Section 5.4) plasmalemma repair. Nevertheless, blocking lysosomal exocytosis through treatment with vacuolin-1 [129], tetanus toxin [130], or cholesterol depletion [130], fails to completely abrogate Ca^{2+}-dependent exocytosis, which suggests that other vesicular compartment may also be involved. Indeed, vesicles derived from the TGN have been shown to be implicated in the facilitated response of cell membrane resealing [101,103]. Another vesicular candidate is the enlargeosome, which also have been shown to undergo regulated exocytosis in response to Ca^{2+} [130,131], or cell wounding [129].

Enlargeosomes are distinct from the endoplasmic reticulum, Golgi, TGN, endosomes, lysosomes and constitutive secretion vesicles. They are identified as small, AHNAK-positive vesicles [130]. AHNAK [132] is a very large (≈700 kDa) protein involved in a variety of distinct functions such as the formation of the blood–brain barrier, cell morphology, cell signaling through is ability to bind both PKC and phospholipase C-gamma (PLCγ), cell migration, formation of cell–cell contacts, regulation of cardiac calcium channel, and many other pathologies (reviewed in [133]). Enlargeosomes are also partly defined by annexin II, which localizes to the cytosolic-face of their membrane and is necessary for their Ca^{2+}-dependent exocytosis [134]. The membranes of enlargeosome have been shown to be resistant to the detergent Triton X-100, and to be rich in cholesterol and sphingolipids [130].

Fusion of enlargeosomes with the plasmalemma has been shown to be dependent on VAMP4 and to involve Syntaxin-6 and SNAP-23 [135]. Enlargeosomes may also interact with the plasmalemma via AHNAK, as it is known to bind the membrane S100A10:annexin II heterotetramer (2:2) [136] in a Ca^{2+}-dependent manner [137,138]. These observations are somewhat problematic, as prior to Ca^{2+}-stimulation, AHNAK is found in the luminal-face of enlargeosomes [139]. AHNAK must therefore be transported across enlargeosome membrane before its exocytic fusion [134], in a as of yet unidentified mechanism.

The exact nature of the contribution of enlargeosome exocytosis to plasmalemma repair is still somewhat ill-defined. Enlargeosomes could indeed potentially be involved in plasmalemma repair in many ways: they have been proposed to be able to add significant amount of membrane components to the injured plasmalemma [139], and to modify plasmalemma content and structure [131] upon exocytic fusion. The role of enlargeosomes in plasmalemma repair could also be linked to the ability of the AHNAK:S10010A10:annexin II complex to modulate actin cytoskeleton organization and cell membrane architecture, in a similar way to what is observed during the formation of cell–cell contacts and the development of epithelial polarity [140]. Several observations also suggest that enlargeosome- and dysferlin-mediated plasmalemma repair may be closely related. Indeed, dysferlin have been shown to interact with AHNAK through its C2A domain [117,141–143], and both proteins co-localize to the sarcolemmal membrane and T-tubules of normal skeletal muscle [143]. Reduction or absence of dysferlin observed in the muscle of dysferlinopahties such as LGMD2B and Miyoshi myopathy correlates with a secondary muscle-specific loss of AHNAK [143]. Furthermore, knockdown assays performed with siRNA directed against AHNAK or dysferlin, equally diminished lysosome fusion to the cell membrane upon Fas Ligand [142]. Finally, calpain-3 cleavage of AHNAK renders it no longer able to bind dysferlin. AHNAK accumulates when calpain 3 is defective in skeletal muscle of LGMD2A patients [126], but nonetheless retains proper AHNAK localisation [144]. Conversely, in LGMD2B muscle, characterized by mutations in dysferlin [38], it is lost to the shedding of AHNAK-positive vesicle into the extracellular environment [126,144].

5.4. Bouncing back: inside-in repair mechanisms

5.4.1. Caveolae-mediated endocytosis of pore-forming proteins

Injury-induced exocytosis has been proposed to restore the membrane barrier function trough the formation of a "patch", or decreased apparent membrane tension followed by spontaneous resealing. However, neither the "membrane patch" nor decreased apparent membrane tension models can explain the removal of transmembrane pores such as SLO [145], pneumolysin (PLY) [146], or perforin [147]. How then, does exocytosis mediates the Ca^{2+}-dependent repair of pore forming toxins or of complement derived pores? The first clue came from the fact that repair of SLO-damaged membranes can be inhibited by cholesterol depletion [148], which is known to inhibit caveolae- [63] and clathrin-mediated [149] endocytosis. SLO pores were also shown to be directly removed from the surface of the plasmalemma via caveolae-dependent endocytosis that results in the lysosomal degradation of the SLO pores [150]. Surprisingly, several experiments showed that caveolae-mediated repair of SLO lesions do not rely on dynamin-dependent mechanism in order to initiate the endocytosis of caveolae (reviewed in [151]). Indeed, dynamin depletion did not affect caveolae formation or the cells removal of SLO as shown by FM1–43 and propidium iodide assays [150]. Instead, exocytic release of ASM was found to be sufficient to induce caveolae-associated SLO lesion repair [109,150]. ASM release to the outer leaflet of the plasmalemma triggers the formation tightly packed ceramide-rich platforms which have been shown to be sufficient for to trigger invagination of the plasmalemma [152], and formation of caveolae-derived endosomes (reviewed in [62]).

5.4.2 . Caveolae-mediated plasmalemma invagination: resealing of large mechanical lesions

Repair of large mechanical lesions have also been shown to be dependent on ASM release and presence of caveolins. Indeed, cells from Niemann–Pick patients (types A and B are linked to ASM deficiency through mutations in SMPD1; reviewed in [153]) are able to undergo Ca^{2+}-dependent exocytosis, but show signs of defective plasmalemma repair and are unable to undergo Ca^{2+}-dependent endocytosis [109]. Similarly, caveolin-3 deficiency causes muscle degeneration in mice [115] and mutations in caveolin-3 are known to cause LGMD1C [40] in humans.

There is, however, little to no evidence that may suggest direct removal of mechanical disruptions trough caveolae-mediated endocytosis. Indeed, electron microscopy experiments showed that the

distribution and localization of the caveolae-like endocytic vesicles associated with the repair of SLO and mechanical damage differed substantially. SLO damage is associated with an increase in the number and size of caveolae and of caveolae-derived vesicles along the entire surface of the affected plasmalemma [148,150,154]. On the other hand, they were found to be concentrated next to mechanical disruptions in the case of muscle cells [150], or forming a single and large merged caveolae in the case of wounded primary muscle fibers [150]. Those very large vesicles and invaginations were initially proposed to be the remnants or precursors of the exocytic "patch" proposed to cover and eventually reseal the wound (see Section 4.2). In the model proposed by Corrotte et al. [150] large caveolae endosomes or caveolae-like invaginations are formed as a consequence of the dynamic changes in plasmalemma composition and shape brought about by the combination of exocytosis, release of ASM, and the presence of proteins such as dysferlin and caveolins. Those caveolae-like invaginations eventually grow intracellularly and eventually fuse. It was proposed [150] that subsequent endocytic release of those structures provides a "constriction force" that promotes plasmalemma resealing. As Corrotte et al. [150] correctly pointed out, endocytic repair presents an alternate explanation of the large vesicles observed near mechanical wounds in a variety of cells [78], initially proposed to be the remnants or the precursors of the exocytic "patch" that was presumed to cover and eventually reseal the wound.

5.5. Inside-out repair

Formation of membrane blebs has been observed during the spreading and migration of cultured cells [155], cytokinesis [156] and apoptosis [157], and is associated with local disruption of the actomyosin cortex [158]. All of those events involve dynamic changes in cytoskeletal structures, so it is not surprising that plasmalemma disruptions is also associated with the formation of membrane protrusions that sometimes, leads to shedding events.

5.5.1. Ectocytosis of transmembrane pores

Recent experiments showed that SLO-pores were successfully removed from the neurites of SH-SY5Y neuroblastoma cells, which are free of lysosomes [159]. The contribution of other membrane compartment such as the enlargeosome and the TGN to bleb formation remains to be investigated, but their contribution is expected to be minimal. Experiments measuring tether forces of blebbing cells provided evidence that membrane blebs are formed as a consequence of local cortical disruption and the contraction by myosin II around the disruption. In accordance with what was observed in the neuroblastoma cells, addition of membrane component alone did not facilitate the formation of membrane blebs [156]. It thus appears that bleb formation do not depend on in plane tension, but is related to the tether force that links the plasmalemma to the cytoskeleton. This hypothesis is further supported by the fact that formation of membrane blebs can be initiated by laser ablation of the cortex cytoskeletal structures [160] and by direct measurements of the thickness of actin cortex in retracting blebs [158]. This also explains why blebbing has been shown to occur irrespective of exocytosis [159,161] or endocytosis [161], and why extensive depolymerization [162] or stabilization [163] of the actin cytoskeleton inhibits the formation of membrane blebs. The formation of membrane blebs can therefore be conceptualized as a relatively passive process where localized actin cytoskeleton disruptions lead to a compression of the cytoskeletal network, and to the release of portions of the plasmalemma which are then inflated by intracellular osmotic pressure [24,156].

EM observations suggest that the blebs involved in SLO shedding are rather small, devoid of normal protein content, and laden with clustered SLO-pores [161]. Equally intriguing is the fact that prefixation of cells with aldehydes before exposure to SLO do not seem to modify the clustering of SLO to blebs [161], suggesting that SLO clustering to membrane blebs may be a passive process. The same authors replaced the Ca^{2+} present in their fixative with Mg^{2+} or EGTA and were unable to observe changes in SLO insertion, pore assembly, or segregation of SLO pores. The observations made by Keyel et al. [161] strongly suggests that SLO pore insertion, pore assembly and pore clustering are Ca^{2+}-independent. The authors also concluded that bleb-formation could also be Ca^{2+}-independent. This is controversial however, as it implies that SLO assembly alone could be sufficient to lower plasmalemma–cytoskeleton interaction and induce the formation of blebs, even in fixed cells. While SLO pore could possibly displace proteins responsible of the interaction of the plasmalemma with the cytoskeleton, the fixation process could also have produced artefactual membrane blebs, which may be more receptive to SLO pore insertion and assembly. This also poses a problem, as other teams have shown that both Ca^{2+} [164] and actin disruption [159] were necessary for the survival of SLO-treated cells [164], and for the shedding of microvesicles [159].

In the model proposed by Atnassoff et al. [159], SLO perforation elevates local Ca^{2+} concentration which in turn activates annexins and calpains. As previously discussed (see Sections 3.1 and 5.2), calpains disrupts the underlying actin cytoskeleton, which in turn facilitates bleb formation and shedding. Annexins may also sequester the damaged membrane by plugging the neck of the bleb formed by myosin II contraction, which limits entry of Ca^{2+} into the cell [164]. This last study did not include direct observation of SLO pores, and is unable to give any insight on the contribution of annexins and cortical contraction to the clustering of SLO pores observed by Keyel et al. [161]. Additional experiments are therefore needed in order to assess whether SLO-pore can directly influence plasmalemma–cytoskeleton interactions, or if SLO-pores preferentially assemble on pre-existing blebs or areas of weak plasmalemma–cytoskeletal interactions. Whether SLO-pores are shed as individual units or in clusters also remain to be fully demonstrated.

While the mechanism involved in the actual shedding of the SLO-laden blebs is known to also be Ca^{2+}-dependent, it may differ depending on the intensity of the SLO injury. Indeed, the shedding of individual SLO-lesions have been proposed to be a thermodynamically favored spontaneous event [159], but this have yet to be directly verified. The mechanism involved in the shedding of the cluster of SLO-laden blebs, while also Ca^{2+}-dependent, is similarly unknown [161].

Ectocytosis is thus probably best seen as a first line of defense against pore-mediated injuries, happening whenever or wherever exocytosis does not occur or in the case of low-damage conditions. This would similarly explain why the prevalence of endocytic and ectocytic repair of SLO lesions have also been shown to vary according to cell-type, cell compartment, the severity and localization of SLO damage and the presence of secondary mechanical damage [148,159,161].

Blebbing events have also been associated with mechanical injury, but have traditionally been associated with apoptosis [157]. Their transient nature precludes them from been involved in actual membrane healing events, although it has been suggested that may be a form of stress response that may give the cells some protection against incoming complement or bacterial pore plasmalemmal insults [164].

5.5.2. Shedding-mediated repair: ESCRT complex

Although it does not involve the formation of true membrane blebs, a recent study by Jimenez et al. [75] recently challenged the view that mechanical lesions could not be removed via excision of the damaged portion of plasmalemma. Indeed, ESCRT-III proteins were shown to be recruited to laser-injured portions of the plasmalemma of HeLa cells and to contribute to the survival of cells bearing small wounds (<100 nm), through budding and shedding of ESCRT-positive vesicles.

The membrane deformation and abscission events mediated by the ESCRT complex involve the sequential recruitment and assembly of several ESCRT subcomplexes (reviewed in [1]). Briefly, ESCRT activity is initiated by ESCRT-0 proteins, which in turn recruits ESCRT-I proteins such as TSG101. ESCRT-II proteins or their functional equivalents act as an adaptor complex between ESCRT-Is and the ESCRT-III subunits.

Assembly of the ESCRT-III complex, composed of charged MVB proteins (CHMPs), into helical filaments is responsible for most of the membrane deformation and fission properties of the ESCRT complex [165]. Abscission is also facilitated by ESCRT-IV disassembly subunits such as Vps4 (reviewed in [166]). The different ESCRT-0, ESCRT-I and ESCRT-II proteins or functional equivalents are therefore responsible for targeting ESCRT-III to specific cellular compartments in order to function. Viral budding, cytokinesis and membrane repair occur in vastly different cellular environment from multivesicular body genesis, so it is not surprising that ESCRT would be recruited via alternate molecular players. For example, viral budding and cytokinesis do not involve ESCRT-0 or ESCRT-II. Instead, the HIV structural protein Gag (reviewed in [167]) and the centrosomal protein CEP55 [168] replace ESCRT-0 in viral budding and cytokinesis respectively, and ALIX acts as an ESCRT-II in both events (reviewed in [165]).

A series of knockdown experiments showed that ALG-2 was the main initiator of ESCRT recruitment during ESCRT-mediated plasmalemma repair. Indeed, it was proposed to act in a similar ways as CEP55, first recruiting ALIX to the wound site, which in turn is necessary for the recruitment and assembly of the ESCRT-III complex and later, of Vsp4 [49,75]. Transport of the ESCRT complex is energy independent, and is not inhibited by nocodazole, meaning that it does not depend on microtubule vesicular transport or exocytic processes [75]. The mechanism involved in the initial recruitment and accumulation the ALG-2/ALIX complex to the wound site is still unclear, but probably primarily involves ALG-2 [49].

ESCRT-mediated repair may also be involved of the repair in a wide range of wounds, as Scheffer et al. [49] reported ESCRT recruitment to plasmalemma disruptions stemming from large (>1 μm) membrane disruptions, and Jiminez et al. [75] reported ESCRT-mediated repair of small (<100 nm) mechanical lesions, or of lesions caused by pore forming molecules such as digitonin, saponin, SLO and listeriolysin O. Lack of experimental evidence nonetheless makes it difficult to assess if ESCRT-mediated repair should be considered as an entirely independent repair mechanism, or if it requires the additional membrane components provided by exocytic events for membrane deformation and abscission (see Fig. 1). ESCRT recruitment to the sites of SLO-lesions may also provide a mechanism by which SLO-derived blebs are shed, and provide an explanation for the paradoxical vesicle release sometimes associated with endocytic repair of large wounds.

5.5.3. Excision-mediated repair: S100A11:annexin 2 complex

While S100A11 was classically thought to primarily form complexes with annexin I [169,170] or annexin VI [171,172], NMR studies have shown that S100A11 interact with annexin II with 5-fold tighter interaction to that of annexin I [173]. This S100A11:annexin II complex has been shown to be important for the survival of invasive cancer cells [51,174], where it was proposed to organize repair by excision of the damaged part of the plasmalemma [51]. Briefly, the mechanism proposed by Jaiswal et al. [51] involves stabilization of the wound-site by annexin I (without S100A11's involvement), followed by the Ca^{2+}-dependent formation of the S100A11:annexin II complex and its accumulation proximal to the injury site. Excision of the damaged portion of the membrane was proposed to be mediated by the conjunction of actin depolymerisation at the wound site which facilitates collapse and separation of the wounded membrane, and actin polymerization by the S100A11:annexin II underneath the wound-site, which aids membrane fusion and re-establishes in plane membrane tension and tether forces that complete wound closure [51]. Recruitment of the S100A11:annexin II was not investigated by Jaiswal et al., but Ca^{2+}-dependent transport of S100A11 was previously shown to require tubulin [175].

6. The actomyosin purse-string

In *Xenopus* [12], sea urchin [176], syncytial *Drosophila* embryo [177], and embryonic epithelial cells [178], plasmalemma resealing is followed by cytoskeleton wound closure and regeneration. This is achieved by the formation and contraction of an actomyosin purse-string that also "pulls" the plasmalemma inward [17]. Despite their similarities, models of *Xenopus* and *Drosophila* actomyosin ring formation differ in regards of the specifics concerning microtubules involvement [179], as well as the specifics of Rho GTPases coordination [177].

In the *Xenopus* oocyte, the formation of the contractile array is controlled by the Ca^{2+}-dependent recruitment and activation of Cdc42 and RhoA to mutually exclusive, concentric zones around the wound [180]. Formation of these Rho GTPase zones are upstream of the formation of the contractile ring and follows the contractile array as it closes [180]. The so-called "RhoA zone" can be found at the wound edge and controls contraction of the array through the activation of myosin-2 and formin, and the formation of unbranched F-actin. RhoA acts via downstream effectors such as Rho associated kinase (ROCK). The Cdc42 zone encircles the RhoA zone, and controls the formation of a region of highly dynamic actin through downstream factors such as N-WASP and p21-activated kinases which controls Arp2/3-dependent assembly of a branched actin network. Once recruited and assembled at the wound site, myosin-based contractility drives cortical flow of stable F-actin to the wound and transport of microtubules to the wound-edge where they buckle and are broken by actomyosin contractility. Microtubules assembly may also be complemented by actin-independent mechanisms that are initiated upon wounding. The high concentration of microtubules ends helps sequester actin and myosin-2 assembly to the wound edge, resulting in a positive feed-back loop of actin recruitment and assembly at the wound edge [13,15,181].

While contraction events are important for the translocation of F-actin and of myosin-2, contraction-mediated shorting is not the only driving force regulating closure of the array or of the RhoA zone [182]. Rather, closure is regulated by a "signal treadmill" involving a preferential activation of RhoA to the leading edge of the wound [182]. Activity of RhoA and Cdc42 also depends on their activation by guanine exchange factors (GEFs) and inactivation by GTPase activating proteins (GAPs) [183], while segregation of both pathways suggests crosstalk. While several GEFs and GAPs have been identified for the regulation of Rho GTPases during the cytoskeletal reorganization events that occurs during events such as cell migration [184], stretch-induced reorientation of vascular endothelial cells [185], and cytokinesis [186], only Abr, a dual GEF-GAP, proved to be an acceptable candidate for single-cell wound repair [187], and its depletion was shown to attenuate Rho activity, as well as wound repair [187]. Formation of a local positive feed-back loop between Abr and RhoA was further suggested to account for the maintenance and dynamic properties of the "RhoA zone", while maintenance and progression of the Cdc42 seemed to be Abr-independent [177].

7. Hypotheses and future perspectives

The last decade led to the identification of many exocytic vesicles and mechanisms involved in plasmalemma resealing, but also led to several apparently conflicting observations, where similar injuries were in the past presented in a way that made it seem that they were repaired by sometimes widely different mechanisms. As the last decade has shown, exocytic and endocytic membrane repair are causally connected, and even share molecular machinery. Therefore, the different membrane repair mechanisms identified so far are best seen as an interconnected pathway, where the type and size of wound dictate the mechanism by which plasmalemma repair occurs, through their impact on the severity of changes in in-plane membrane tension (i.e., increase plasmalemma area) and membrane tether forces (see Fig. 1). For example, SLO pores create a uniformly elevated Ca^{2+} concentration across large portion of the membrane, which in addition may also affect overall membrane tension, through cytoskeletal depolymerization and tonicity-mediated changes in cell volume. This would create a generalized activation of the repair process that can act across the membrane as a whole and allow for the removal of pores across the plasmalemma.

Electroporated or osmosis-damaged cells also present many small wounds across large portions of their plasmalemma and probably reseal their membrane in a similar fashion. The Ca^{2+} gradients created by mechanical lesions are comparatively more localized, and might be accompanied by a localized modification of plasmalemma composition and an increased plane membrane tension. This localized Ca^{2+} entry would presumably help target exocytosis, ASM release and formation of large caveolae-like plasmalemma invagination to the wounded area of the plasmalemma [150].

In mammalian cells, Rho GTPases could also be recruited by AHNAK upon the Ca^{2+}-dependent exocytosis of enlargeosomes, as AHNAK has been shown to be able to activate PKC through dissociation of the PKC-protein phosphatase 2A complex [188]. Similarly, formation of ceramide-rich membrane domains may also leads to Rho GTPases helping in F-actin remodeling. Indeed, formation of C(16) ceramide was wound to be able to increase PKC phosphorylation, and subsequent activation of the N-WASP/Cdc42/Arp2/3 pathway and modification of the actin cytoskeleton [64]. As such, independent of their role in the control of surfactant synthesis, enzymes implicated in ceramide production may also contribute to adult respiratory distress syndrome (ARDS) and RDS of the neonate, in adult and premature infants, chronic obstructive pulmonary disease, as well as bronchopulmonary dysplasia, trough altered actin recruitment upon plasmalemma injury.

The regions of PIP_2-, PIP_3-, PS-, PA- and DAG-enriched plasmalemma forming upon wounding described by Vaughan et al. [61] are of particular interest as they may constitute the upstream signal for the activation of RhoA and Cdc42 at specific areas of the wounded plasmalemma. Having only been observed in *Xenopus*, it would be interesting to see if similar lipid-defined plasmalemmal regions are also formed in sea urchin oocytes, syncytial drosophila embryo, or embryonic epithelial cells. Similarly, considering that the cells type that are exposed to the most mechanical damage events are also under the most mechanical tension from extracellular sources (muscle, lung), and that Rho GTPases and their downstream effectors, are known to be modulated in cells undergoing stretch-induced differentiation [189], one can ask if the initial tensegrity state of the cell (i.e., high mechanical load from an external source vs low mechanical load) or its rapid change, before or at the time of injury play a role in injury repair. This could yield considerable information for wound healing and the initiation of cytokinesis.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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